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Association of Thyroid functions with components of Metabolic syndrome: A case control study from North India

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ABSTRACT

Background: Metabolic syndrome and thyroid dysfunction (TD) are independent risk factors for the development of atherosclerotic Cardiovascular Disease (CVD), concurrent existence of both may further compound the increased risk of cardiovascular event in the same individual. Therefore, our study aimed to evaluate the thyroid profile in patients with MetS and to explore the relationship between thyroid function tests and components of metabolic syndrome.

Methods: This case control cross sectional study included 100 patients aged 20 years and above with metabolic syndrome as per the criteria recommended by IDF (The International Diabetes Federation) panel and 100 age and sex matched controls. Patient's anthropometric measures like weight, height, BMI, and waist circumference and blood pressure along with detailed medical history were recorded in a prescribed proforma. Fasting venous blood samples (5 ml) was collected and analyzed for triglycerides, high density lipoprotein (HDL) cholesterol, free triiodothyronine (T3), free thyroxine (T4) and thyroid stimulating hormone (TSH). Blood glucose, triglycerides and total cholesterol were measured by enzymatic method. HDL cholesterol by homogeneous, direct method. Serum free T3 (1.4-4.2 pg/dL), free T4 (0.8-2.0 ng/dL) and TSH (0.28-6.82 μIU/dL) were measured by using CLIA on ADVIA Centaur.

Results: The study analyzed 200 subjects, with 100 in the case group and 100 in the control group. Results showed higher systolic and diastolic blood pressure, abdominal circumference, fasting glucose, total cholesterol, triglycerides, and LDL, while lower HDL levels. The case group had a higher prevalence of thyroid disorders, with subclinical hypothyroidism being the

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

most common. Abdominal obesity was found to be associated with thyroid dysfunction, while male gender showed significant negative association with thyroid dysfunction. **Conclusion:** Metabolic syndrome patients often have thyroid dysfunction, particularly subclinical and overt hypothyroidism, with females at higher risk. This may increase their risk of CVD. Screening for thyroid dysfunction is crucial for early intervention and better management. Future prospective studies should explore the cause-effect relationship.

Key-words: Metabolic syndrome, thyroid dysfunction, cardiovascular disease, IDF panel, hypothyroidism.

INTRODUCTION

Metabolic syndrome (MetS) comprises of certain risk factors namely, atherogenic dyslipidemia, hypertension, glucose intolerance, central obesity which are prothrombotic and pro-inflammatory conditions, that ascertain the increased risk of atherosclerotic cardiaovascular disease and type 2 diabetes [1, 2].

The prevalence of MetS is increasing across the globe owing to different regions having distinctive arrays of epidemic risk factors, and a remarkable increase in its prevalence has been noted in India as well attributing to increased migration to urban areas, mechanization, socioeconomic transitions towards increased affluency [3-5].

Thyroid diseases are among the most prevalent endocrine disorders worldwide. Based on the estimation from various studies, it has been projected that about 42 million people in India suffer from thyroid diseases [5]. Since thyroid hormones play an important regulatory role in lipid metabolism, glucose metabolism, blood pressure and cardiovascular function, any dysregulation in thyroid function might be associated with MetS as both are charachetrized by overlapping common abnormalities such as hyperglycemia, hypertension, reduced high-density lipo-protein cholesterol (HDL-C), and elevated triglycerides, insulin resistance and obesity [6, 7].

As both metabolic syndrome and thyroid dysfunction (TD) are independent risk factors for the development of atherosclerotic Cardiovascular Disease (CVD), concurrent existence of both may further compound the increased risk of cardiovascular event in the same individual [8].

Several studies done in past on thyroid disorders in metabolic syndrome about its prevalence and its association with components of metabolic syndrome results have shown varied results and have been controversial [9, 10]. Thyroid function tests may be required to be done in metabolic syndrome to assess the increased compounded risk of cardiovascular disease due to the concurrent presence of both if any. Therefore, our study aimed to evaluate the thyroid

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

profile in patients with MetS and to explore the relationship between thyroid function tests and components of metabolic syndrome that may guide in better planning and management of MetS patients' treatment leading to decreased morbidity and mortality due to cardiovascular events in them.

MATERIALS AND METHODS

Study Design

This case control cross sectional study was conducted in department of biochemistry and Dept of medicine at, Rohilkhand medical college and hospital, Bareilly, UP after getting approval by the ethical committee of the institute.

Study Population

The sample size was taken as per the convenience of the study. All 100 patients aged 20 years and above with metabolic syndrome as per the criteria recommended by IDF panel attending the hospital either as outpatients or inpatients in General medicine ward were included in the study after obtaining their informed consent. Age and sex matched 100 controls were also taken from the same hospital. Patients with a cardiovascular disease, any liver disorder, and renal dysfunction, pregnant females, patients on OC pills and other medications that alter thyroid functions and lipid levels were excluded from the study.

IDF criteria include central obesity (defined as waist circumference $\geq$90 cm for men and $\geq$80 cm for women, with ethnicity specific values for other groups) plus any two of the following four factors:

- raised TG levels: $\geq$150 mg/dL or specific treatment for this lipid abnormality.
- reduced HDL cholesterol: <40 mg/dL in males and <50 mg/dL in females, or specific treatment for this lipid abnormality
- raised blood pressure: Systolic BP $\geq$130 or diastolic BP $\geq$85 mm Hg, or treatment of previously diagnosed hypertension.
- raised fasting plasma glucose (FPG) $\geq$100 mg/dL, or previously diagnosed type 2 diabetes.

Examination

Patient's anthropometric measures like weight, height, BMI, and waist circumference and blood pressure along with detailed medical history were recorded in a prescribed proforma.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

Biochemical investigations

Fasting venous blood samples (5 ml) was collected and analyzed for triglycerides, high density lipoprotein (HDL) cholesterol, free triiodothyronine(T3), free thyroxine (T4) and thyroid stimulating hormone (TSH). Blood glucose, triglycerides and total cholesterol levels were measured by enzymatic method on EM -360 analyzer. HDL cholesterol by homogeneous, direct method. Serum free T3(1.4-4.2 pg/dL), free T4 (0.8-2.0 ng/dL) and TSH (0.28-6.82 μIU/dL) were measured by using CLIA on ADVIA Centaur. Patients were said to be euthyroid if all thyroid hormone levels fell within reference range. Overt hypothyroidism was defined as raised TSH and low free T3 and free T4. Subclinical hypothyroidism was considered if TSH was raised with free T3 and free T4 within reference range. Subclinical hyperthyroidism was defined as TSH low with free T3 and free T4 within reference range and secondary hypothyroidism was considered when TSH was observed to be normal or low with low fT4 levels.

Statistical Analysis

Statistical analysis was performed with the help of software SPSS version 21.0. Graphs and tables were made by using Microsoft excel 2007. Categorical variables were presented as numbers and percentages. All descriptive data was expressed as Mean ± standard deviation and percentages. Independent sample t test and one way ANOVA was applied for continuous variables and chi square test for categorical variables at 95 % confidence interval. Pearson's correlation was performed to find out the relation between different continuous variables. For all statistical analyses $p<0.05$ was considered statistically significant.

RESULTS

A total of 100 (50%) subjects enrolled in the study fulfilled the criteria of metabolic syndrome according to IDF definition and comprised the case group of the study whereas remaining 100 (50%) subjects enrolled in the study were individuals who did not have metabolic syndrome and comprised the control group of the study.

In both the groups, maximum number of cases were aged 51 to 60 years and minimum were aged >60 years. Mean age of patients in case group was 46.58±10.73 years (range 20-65 years) whereas mean age of controls was 43.44±12.07 years (range 21-65 years). Statistically, there was no significant difference between two groups with respect to age (p=0.052).

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

Irrespective of the group, majority of subjects were females. Statistically, no significant difference was observed between two groups (p=0.564).

Table 1: Comparison of two study groups for hemodynamic parameters

SN	**Parameter**	**Cases**		**Control**		**Statistical significance**	
		Mean	**SD**	**Mean**	**SD**	**'t'**	**'p'**
1.	SBP (mm of Hg)	137.68	14.20	124.62	7.79	8.064	<0.001
2.	DBP (mm of Hg)	84.94	6.89	79.25	4.97	6.698	<0.001

Both systolic as well as diastolic blood pressure levels of the cases were found to be significantly higher as compared to that in control group (p<0.001).

Table 2: Comparison of two study groups for Anthopometric and Biochemical Parameters

SN	**Parameter**	**Cases**		**Control**		**Statistical significance**	
		Mean	**SD**	**Mean**	**SD**	**'t'**	**'p'**
1.	Abdominal circumference (cm)	101.11	9.14	88.10	10.55	9.319	<0.001
2.	Fasting glucose (mg/dl)	166.12	54.45	94.24	14.78	12.739	<0.001
3.	Total cholesterol (mg/dl)	223.73	40.64	204.20	37.04	3.552	<0.001
4.	Triglyceride (mg/dl)	204.86	68.93	130.66	38.34	9.407	<0.001
5.	HDL (mg/dl)	43.93	10.28	52.98	5.69	-7.706	<0.001
6.	LDL (mg/dl)	138.82	38.27	125.09	33.27	2.708	0.007

Mean abdominal circumference, fasting glucose, total cholesterol, triglyceride and LDL levels of cases were significantly higher as compared to controls whereas mean HDL levels of cases were significantly lower as compared to that of controls.

Table 3: Comparison of two study groups for factors of metabolic syndrome

ISSN: 0975-3583, 0976-2833 **VOL15, ISSUE 01, 2024**

SN	**Parameter**	**Cases**		**Control**		**Statistical significance**	
		No.	**%**	**No.**	**%**	**χ^2**	**'p'**
1.	Abdominal obesity	100	100	51	51	64.90	<0.001
2.	Hypertension	75	75	18	18	65.30	<0.001
3.	Raised Glucose	91	91	28	28	82.35	<0.001
4.	Raised Triglyceride	79	79	25	25	58.41	<0.001
5.	Low HDL	65	65	11	11	61.89	<0.001

Abdominal obesity was seen in 100% cases as compared to 56% controls, thus showing a statistically significant difference between two groups (p<0.001).

For all the other factors of metabolic syndrome too, cases had a significantly higher proportion as compared to controls (p<0.001).

Among cases, maximum (n=38; 38%) were positive for all the five metabolic syndrome factors followed by 34 (34%) who were positive for four factors and a total of 28 (28%) were positive for 3 factors whereas among controls, 17 (17%) were positive for none of the metabolic factors, 33 (33%) were positive for 1 factor and 50 (50%) were positive for 2 metabolic syndrome factors.

Table 4: Comparison of Thyroid functions between two study groups

SN	**Parameter**	**Cases**		**Control**		**Statistical significance**	
		Mean	**SD**	**Mean**	**SD**	**'t'**	**'p'**
1.	TSH	4.24	2.47	3.35	2.36	2.602	0.010
2.	fT_3	2.76	0.97	3.01	0.81	1.995	0.047
3.	fT_4	0.97	0.37	1.38	0.38	7.641	<0.001

Mean levels of TSH levels were significantly higher in cases as compared to controls (p<0.001) and mean levels of T3 and T4 (including fT3 and fT4) were significantly lower in cases than that of controls.

Among cases, prevalence of thyroid disorders was 32%. Subclinical hypothyroidism was seen in 29 (29%) cases, secondary hypothyroidism in 1 (1%) and subclinical hyperthyroidism in 2

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

(2%) cases. In control group, only 7 (7%) had thyroid disorder – all these had subclinical hypothyroidism. Statistically, the difference between two groups was significant ($p<0.001$).

Table 5: Association between Thyroid disorders and Different factors of metabolic syndrome

(a) Cases

SN	Factor	Positive			Negative			Statistical significance
		Total	With thyroid disorder	% with thyroid disorder	Total	With thyroid disorder	% with thyroid disorder	
1.	Abdominal obesity	100	32	32.0	-	-	-	-
2.	Hypertension	75	22	29.3	25	10	40.0	χ^2=0.980; p=0.322
3.	Raised glucose	91	29	31.9	9	3	33.3	χ^2=0.008; p=0.928
4.	Raised Triglyceride	79	27	34.2	21	5	23.8	χ^2=0.820; p=0.365
5.	Low HDL	65	19	29.2	35	13	37.1	χ^2=0.654; p=0.419

(b) Controls

SN	Factor	Positive			Negative			Statistical significance
		Total	With thyroid disorder	% with thyroid disorder	Total	With thyroid disorder	% with thyroid disorder	
1.	Abdominal obesity	51	7	13.7	49	0	0	χ^2=7.232; p=0.007
2.	Hypertension	18	1	5.6	82	6	7.3	χ^2=0.070; p=0.791
3.	Raised glucose	28	1	3.6	72	6	8.3	χ^2=0.702; p=0.402

ISSN: 0975-3583, 0976-2833 **VOL15, ISSUE 01, 2024**

4.	Raised Triglyceride	25	3	12.0	75	4	5.3	χ^2=1.280; p=0.258
5.	Low HDL	11	2	18.2	89	5	5.6	χ^2=2.374; p=0.123

In Case group, all the patients had abdominal obesity. Prevalence of thyroid disorder in case group was 32%. Thus, prevalence of thyroid disorder among obese patients was 32%.

In control group, abdominal obesity was seen in 51 cases, of whom 7 (13.7%) had thyroid disorder namely subclinical hypothyroidism as compared to none without abdominal obesity. Thus, showing a statistically significant association (p=0.007).

For other factors, no statistically significant association between factor and prevalence of thyroid disorder was observed both in case and control groups (p>0.05).

Table 6: Association between Thyroid disorders and Age

SN	**Factor**	**With thyroid disorder**			**Without thyroid disorder**			**Statistical significance**
		n	**Mean**	**SD**	**n**	**Mean**	**SD**	
1.	Cases	32	49.22	8.86	68	46.47	9.77	t=1.350; p=0.180
2.	Controls	7	34.71	11.63	93	42.18	12.96	t=1.480; p=0.142

No significant association was observed between age and thyroid disorders in both the groups.

Table 7: Association between Thyroid disorders and Gender

SN	**Factor**	**Male**			**Female**			**Statistical significance**
		Total	**With thyroid disorder**	**% with thyroid disorder**	**Total**	**With thyroid disorder**	**% with thyroid disorder**	
1.	Cases	38	7	18.4	62	25	40.3	χ^2=5.194; p=0.023
2.	Controls	42	0	0	58	7	12.1	χ^2=5.451; p=0.020

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

For cases and controls independently, prevalence of thyroid disorders was higher in females as compared to males and this association was significant statistically too ($p<0.05$).

Table 8: Binary Logistic Regression to see the association of thyroid dysfunction with different metabolic syndrome factors and gender

	B	**S.E.**	**Wald**	**df**	**Sig.**	**OR**	**95.0% C.I. for EXP(B)**	
Male Gender	-1.384	.472	8.599	1	0.003	.251	.099	.632
Hypertension	-.417	.467	.799	1	0.371	.659	.264	1.645
Raised TG	.772	.501	2.373	1	0.123	2.164	.810	5.780
Low HDL	.129	.447	.083	1	0.773	1.138	.474	2.730
Raised glucose	-.622	.684	.827	1	0.363	.537	.141	2.050
Metabolic syndrome	2.107	.823	6.558	1	0.010	8.220	1.639	41.221
Constant	-2.256	.464	23.597	1	<0.001	.105		

In present study, abdominal obesity was found to be an invariable factor associated with thyroid dysfunction. Hence it was excluded from the multivariate assessment. Thus, a binary logistic model was proposed based on the assumption that thyroid dysfunction is dependent on independent variables Gender, Hypertension, Raised TG, Raised Glucose, Low HDL and Metabolic syndrome. Among different independent variables evaluated, male gender had a significant negative association (p=0.003; OR=0.251; 95% CI=0.099-0.632) and metabolic syndrome (p=0.010; OR=8.220; 95% CI=1.639-41.221) had a significant positive association with the outcome¸ *i.e.* thyroid dysfunction.

DISCUSSION

Metabolic syndrome is a constellation of various factors such as obesity, hypertension, dyslipidemia with elevated triglycerides and low values of high-density lipoproteins and hyperglycemia [11]. In our study 100 patients with metabolic syndrome were taken and age of patients ranged from 20-65 years with a mean age of 46.58±10.73 years. As observed in previous studies, our study also supported an increase in proportion of patients with metabolic syndrome with increasing age except in the age group >60 years that could be attributed to a

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

strict exclusion criterion used by us, as it was difficult to find out individuals with metabolic syndrome without any liver disorder, renal disorder, congestive cardiac failure in this age group [12, 13].

Majority of our cases were females (62%) with a male to female ratio of 0.61:1. These observations are similar to established observations that females are at a higher risk to develop metabolic syndrome as compared to males as enumerated in previous studies [14, 15].

Metabolic syndrome factors like abdominal obesity were prevalent in majority of subjects (51%) enrolled in the control group too. Other metabolic syndrome factors like hypertension (18%), raised glucose (28%), raised triglyceride (25%) and low HDL (11%) were also seen in a sizeable number of control subjects as compared to 75%, 91%, 79% and 65% of cases which could be attributed to the sedentary life style of current population influencing the health level of the society.

In present study, we used IDF criteria for evaluation of metabolic syndrome which specifies central obesity to be an integral component of metabolic syndrome. We chose to follow the IDF criteria over NCEP: ATP III (National Cholesterol Education Program Adult Treatment Panel III) because the IDF criteria considers the variation of ethnicity while ATP III is applicable mainly to the American population.

Thyroid hormones play an important regulatory role in lipid and glucose metabolism, blood pressure and cardiovascular function therefore any dysregulation in thyroid function might be associated with Metabolic syndrome [6, 7].

In present study, mean TSH levels were significantly higher in patients affected with metabolic syndrome as compared to control group ($p<0.05$) and mean fT_3 and fT_4 levels were lower than controls and was significant($p<0.05$). Similar results were also observed in other studies conducted from India [16-18]. Prevalence of thyroid disorders (TD) was 32% and 7% respectively in metabolic syndrome and non-metabolic syndrome populations, the difference being statistically significant ($p<0.05$). Among cases, most common thyroid disorder observed was subclinical hypothyroidism (29 patients), one patient had secondary hypothyroidism and 2 with subclinical hyperthyroidism. Among controls, all the 7 had subclinical hypothyroidism. These observations were in agreement with results from other studies done previously [14, 19-21].

Prevalence of thyroid disorder in metabolic syndrome cases in different series ranged from 26% to 78% which could be attributed to use of different criteria for classification of thyroid disorder and metabolic syndrome being used in different studies.

In present study, abdominal obesity was observed as a strong predictor of thyroid dysfunction as even all controls who were found to have thyroid dysfunction had abdominal obesity in

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

common. The association between thyroid dysfunction and obesity is well known, however, whether it is cause or effect remains yet to be explored. In a study evaluating association between thyroid disorder and obesity using a BMI criterion for obesity, as many as 44% of thyroid disorder patients were found to be obese. Conversely, among 450 patients attending an obesity clinic, 44% were found to be having thyroid disorder [22].

In preset study, on evaluating the data for association of independent factors of metabolic syndrome with thyroid dysfunction in patients of MeS, none of the factors were significantly associated with thyroid dysfunction. A few other studies had also the same observations [21, 23, 24]. However, our observations were contrary to results obtained from some previous studies where a significant association was observed [6, 16, 25]. It is to be emphasized that patterns of thyroid disorders in MetS and its association with different components of MetS may vary according to age, gender, genetics, diet, environment and geographical location [1, 26, 27].

In present study, the association between age and thyroid disorder was not found to be significant both in cases and controls independently. However, in our study, women with MetS had a higher incidence of TD in comparison to men (40.3% vs. 18.4%). This agreed with reports from other studies having similar finding [6, 21, 28].

Multivariate logistic regression done in present study revealed that female gender and presence of metabolic syndrome were significantly associated with the outcome, *i.e.* thyroid disorder which is in agreement to the univariate assessment findings. Given the fact, that metabolic syndrome as well as thyroid dysfunction is more common in females in this part of the world, these outcomes seem to be logical and rationalistic. The findings also draw attention towards emergence of thyroid dysfunction as an upcoming major lifestyle threat in view of its strong association with metabolic syndrome which is a major lifestyle disorder. It further warrants establishment of systematic approach towards evaluating the presence of thyroid dysfunction in patients with MetS for better clinical management.

LIMITATIONS

The present study has few limitations. First the sample size was small, which may have affected the correlation between components of metabolic syndrome and thyroid function. Secondly, this is a cross-sectional study, therefore cause and effect of relationship between thyroid disorders and MetS could not be determined.

CONCLUSION

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 01, 2024

Patients of Metabolic Syndrome were found to have high prevalence of thyroid dysfunction namely subclinical hypothyroidism and overt hypothyroidism with females at greater risk. As metabolic syndrome and Hypothyroidism are independent risk factor for Obesity and atherosclerotic diseases, patients of MetS having hypothyroidism may have compounded risk of having CVD. Therefore, it mandates the need of screening such patients for the presence of thyroid dysfunction, which may aid in early intervention and better management of such patients for reducing the risk of adverse cardiovascular event and better outcome. However, future large sample-sized prospective studies are warranted to explore cause and effect relationship between metabolic syndrome and thyroid disorders.

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